Modeling of Chlorpyrifos Exposure, Dose, and Biomarker Using NHEXAS Minnesota Children's Data

Edwin J. Furtaw, Jr.[1], Miles Okino[1], James J. Quackenboss[1], Amit Roy[2], and Paul J. Lioy[2]

1 U.S. Environmental Protection Agency, Office of Research and Development, NERL, HERB, Las Vegas, NV

2 Environmental and Occupational Health Sciences Institute, UMDNJ-RWJ Medical School, Piscataway, NJ

Abstract

Data from the National Human Exposure Assessment Survey (NHEXAS) are now becoming available. For the organophosphorus insecticide chlorpyrifos, available data for NHEXAS Minnesota children include concentrations in air, food, beverages, water, house dust (transferable surface residues), soil, and hand rinses; and 3,5,6-trichloro-2-pyridinol (TCPy), a chlorpyrifos metabolite, in urine. To evaluate these data, we used the environmental measurements as inputs to a dynamic model of chlorpyrifos exposure and human pharmacokinetics. The model simulated the urinary TCPy concentration. Exposure factors were taken from EPA's Office of Pesticide Programs' Draft Standard Operating Procedures for Residential Exposure Assessments and from EPA's Exposure Factors Handbook. Non-dietary ingestion from hand-to-mouth activity, and dermal absorption, collectively accounted for about 84% of the modeled absorbed chlorpyrifos dose. Measured urinary TCPy concentrations exceeded modeled concentrations by a factor of about 6. Possible explanations for this disparity include: additional unmeasured exposure to chlorpyrifos occurred outside the home; actual exposure concentrations were different than those measured due to heterogeneity of residues; exposure factors are missing or incorrect; the pharmacokinetic model (which was based on adult male data) is inappropriate for children; and additional exposure to TCPy itself (which was not analyzed in environmental samples) may have occurred. Of these, the last explanation is supported by other research which has shown that TCPy occurs in agricultural products, and even more so in prepared foods, due to environmental degradation of chlorpyrifos. This possible explanation shows the importance of carefully selecting and matching environmental and biomarker measurements in exposure studies. When the chosen biomarker is a metabolite, consideration must be given to measuring the metabolite as well as the parent compound in environmental samples.

The U.S. EPA Office of Research and Development funded this research. The abstract was reviewed and approved. The presentation has not been reviewed.

Introduction

In the Minnesota Children's Pesticide Exposure Study (MNCPES), a part of the National Human Exposure Assessment Survey (NHEXAS), multimedia exposure-related measurements were made for several pesticides, including the organophosphorus insecticide chlorpyrifos (Quackenboss et al., 2000). Data now available from the MNCPES include chlorpyrifos concentrations in air, food, beverages, water, house dust, soil, and hand rinses; and 3,5,6-trichloro-2-pyridinol (TCPy), a chlorpyrifos metabolite, in urine.

In this project, we assessed the multi-pathway chlorpyrifos exposure of the MNCPES children. This was done by using mean data results from the MNCPES exposure measurements as inputs to a dynamic model that simulates time-dependent absorbed dose rates and urinary TCPy concentration. Objectives of this modeling exercise were to evaluate the relationships of the various measurements to urinary biomarker levels, and to estimate the relative contributions to total absorbed dose from various exposure pathways.

Exposure pathways included in the analysis are inhalation, dietary ingestion, dermal absorption, and non-dietary ingestion resulting from hand-to-mouth activity after the hands have contacted residues on both hard and soft (carpeted) household surfaces. In addition to MNCPES mean data results, other factors used in the model include exposure rate estimates taken from EPA's Office of Pesticide Programs' Standard Operating Procedures (OPP SOP) for Residential Exposure Assessment (EPA 1997a) and from EPA's Exposure Factors Handbook (EFH) (EPA 1997b).

Model Description

The model was programmed using the graphical interface Simulink® in MATLAB® software (MathWorks 1998). The overall model schematic diagram is shown in Figure 1. Each box in this diagram is a subsystem that performs programmed calculations. When a subsystem is opened by double-clicking, another schematic diagram is shown. The subsystem diagram shows the computational scheme and values of each input variable. For example, Figure 2 shows the Dermal Exposure subsystem.

The pharmacokinetic part of the model was calibrated to data from a study by Nolan et al. (1984) in which human volunteers ingested and were dermally exposed to known amounts of chlorpyrifos. Following these exposures, the volunteers' blood and urine were monitored for several days for TCPy (Figure 3). Mean data values from the approximately 96 MNCPES children were then provided as input data to the model. The model was then run reiteratively until a daily steady-state condition was achieved in all mass-containing compartments in the model. Daily steady-state was achieved when the mass in the compartment was the same at the end of a 24-hour day as it was at the beginning of that day.

A sensitivity analysis was performed to evaluate the relative importance of the various input parameters in determining the output result. The sensitivity for a given input parameter is defined as the percent change in urinary TCPy concentration that results from a 100% increase in the value of that input parameter. The table to the right lists the most sensitive parameters.

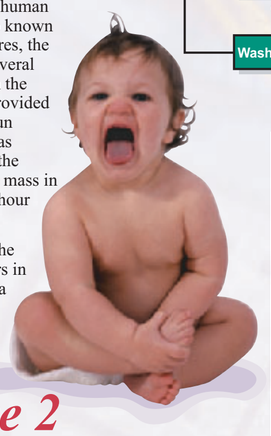
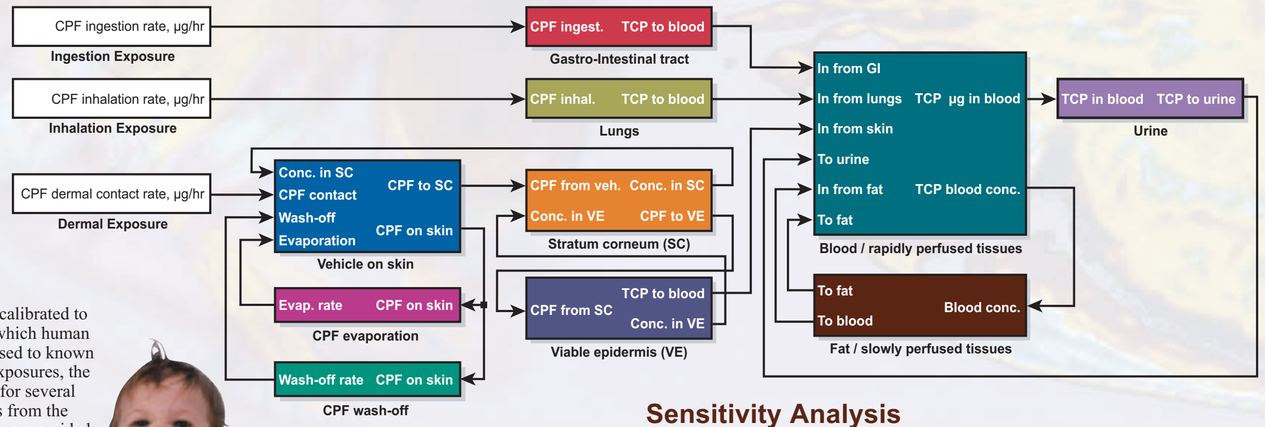


Figure 1

Chlorpyrifos exposure-dose model

CPF = chlorpyrifos TCP = 3,5,6-trichloro-2-pyridinol



Sensitivity Analysis

Showing All Input Parameters with Sensitivity Greater Than 1%

Parameter	Subsystem	Mean Value	Units	Source	Sensitivity
CPF transferrable carpet loading	Dermal Exp. & Ingestion Exp.	0.0009	µg/cm²	MNCPES	+83.5%
GI Fraction absorbed	Gastro-Intestinal Tract	0.7	dimensionless	Nolan et al.	+82.5%
Non-dietary ingestion mouthing rate	Ingestion Exposure	1.56	events/hr	OPP SOP	+68.8%
Non-dietary ingestion area mouthed	Ingestion Exposure	350	cm²/event	OPP SOP	+68.8%
Urine production rate	Urine	0.033333	L/hr	Estimated	-50.0%
Dermal transfer coefficient	Dermal Exposure	8700	cm²/hr	OPP SOP	+14.7%
Skin permeability coefficient	Vehicle on skin	6.0 E-6	cm/hr	Fit to Nolan et al. data	+13.8%
CPF dietary ingestion rate	Ingestion Exposure	0.4	µg/day	MNCPES	+13.7%
Skin deposit thickness	Vehicle on skin	0.00833	cm	Nolan et al.; estimate	-7.7%
Wash-off rate constant	CPF Wash-off	23.105	hr⁻¹	Est. w/wash duration for 50% removal	-6.8%
Urinary elimination rate constant	Urine	0.028	hr⁻¹	Fit to data of Nolan et al.	+4.1%
CPF air concentration	Inhalation Exposure	0.0061	µg/m³	MNCPES	+2.0%
Lung fraction absorbed	Lungs	0.7	dimensionless	Estimated	+2.0%
Active inhalation rate	Inhalation Exposure	0.5264	m³/hr	EPA EFH; estimated	+1.5%
Resting inhalation rate	Inhalation Exposure	0.2632	m³/hr	EPA EFH; estimated	+1.3%
GI absorption rate constant	Gastro-Intestinal Tract	0.3	hr⁻¹	Fit to data of Nolan et al.	-1.3%
Evaporation rate constant	CPF Evaporation	0.01	hr⁻¹	Estimated	-1.1%

Figure 2

Chlorpyrifos exposure-dose model
Dermal exposure module

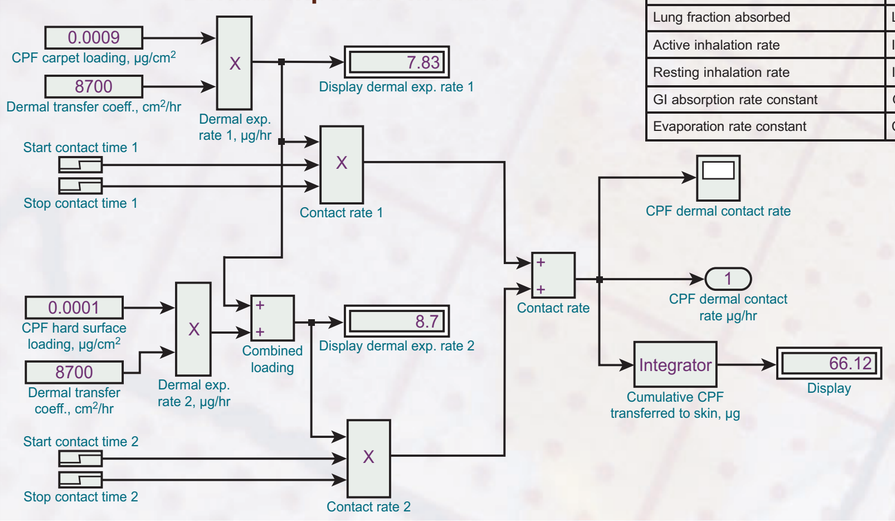
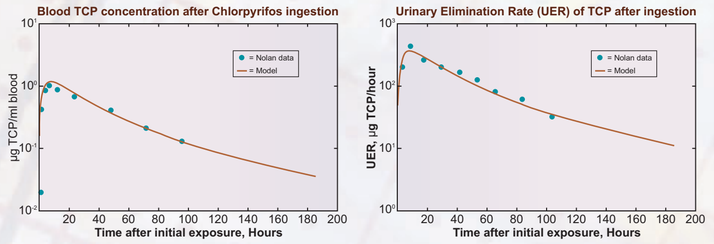


Figure 3



Discussion

Measured urinary TCPy concentrations exceeded modeled concentrations by a factor of about 6. Possible explanations for this disparity include:

- additional unmeasured exposure to chlorpyrifos may have occurred outside the home;
- actual exposure concentrations may have been different than those measured due to heterogeneity of residues;
- exposure factors may be missing or incorrect;
- the pharmacokinetic model (which was based on adult male data) may be inappropriate for children; and
- additional exposure to TCPy itself (which was not analyzed in environmental samples) may have occurred.

Of these, the last explanation is supported by other research which has shown that TCPy occurs in agricultural products, and even more so in prepared foods (Wilson and Morgan, 1999), due to environmental degradation of chlorpyrifos. In that study, TCPy in solid food samples was over an order of magnitude higher than chlorpyrifos in the food samples. This possible explanation shows the importance of carefully selecting and matching environmental and biomarker measurements in exposure studies. When the chosen biomarker is a metabolite, consideration must be given to measuring the metabolite as well as the parent compound in environmental samples.

Conclusions

We draw several conclusions from this research:

- Dermally-mediated pathways dominate children's exposure to chlorpyrifos.
- Non-dietary ingestion resulting from children's hand-to-mouth activity is the major pathway of chlorpyrifos exposure for children.
- Exposures to the chlorpyrifos metabolite TCPy, rather than to chlorpyrifos itself, is probably a major contributor to the TCPy found in children's urine.
- When conducting studies of exposure to chlorpyrifos, simultaneous exposure to TCPy should also be measured.

References

Quackenboss, J.J., Pellizzari, E.D., Shubat, P., Whitmore, R.W., Adgate, J.L., Thomas,K.W., Freeman, N.C.G., Stroebel, C., Lioy, P.J., Clayton, A.C., and Sexton, K. (2000). Design Strategy for Assessing Multi-Pathway Exposure for Children: the Minnesota Children's Pesticide Exposure Study (MNCPES). JEAEE **10**, 145-158.

EPA (1997a). DRAFT Standard Operating Procedures (SOPs) for Residential Exposure Assessments. Office of Pesticide Programs, Wash., D.C.

EPA (1997b). Exposure Factors Handbook, Volume 1 - General Factors. Office of Research and Development, Wash., D.C. EPA/600/P-95/002Fa.

MathWorks (1998). The MathWorks, Inc., Natick, MA.

Nolan, R.J., Rick, D.L., Freshour, N.L., and Saunders, J.H. (1984). Chlorpyrifos: Pharmacokinetics in Human Volunteers. Tox. & Appl. Pharm., **73**, 8-15. Academic Press, Inc.

Wilson, N.K. and Morgan, M.K. (1999). Urinary Biomarkers of Exposure of Several Preschool Children to Pentachlorophenol, Chlorpyrifos, 2,4-Dichlorophenoxyacetic Acid, and Benz[a]anthracene. Presentation at EPA/NIEHS Workshop on Applying Biomarker Research, Chapel Hill, NC.

Results

The time profiles of several important variables are shown in Figure 4. This shows the variation throughout the day of exposures, absorbed dose rates, and urinary TCPy concentration.

Figure 5 is a pie chart that shows the relative contributions from each of the four major exposure pathways. Non-dietary ingestion is the major exposure pathway, accounting for about 68% of the total daily absorbed dose. Dermal absorption is the second most important pathway. These first two pathways, which can be considered collectively as the dermally mediated exposure pathways, account for 84% of the total dose.

The total modeled daily absorbed dose was 2.03 µg/day as chlorpyrifos. Stoichiometrically, this would yield 1.15 µg/day of TCPy, and would result in an estimated urinary TCPy concentration of 1.52 µg/L in the morning-void urine sample. However, the measured mean urinary TCPy concentration in the MNCPES children was 9.17 µg/L. Thus the measured urinary TCPy data exceed the modeled results by a ratio of about 6 to 1.

Figure 4

Multi-Route Absorbed Dose Rates and Urinary TCP Concentration

Scenario based on OPP SOP and EFH exposure factors and mean environmental concentration data from MNCPES children

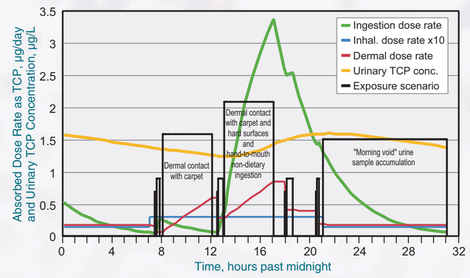
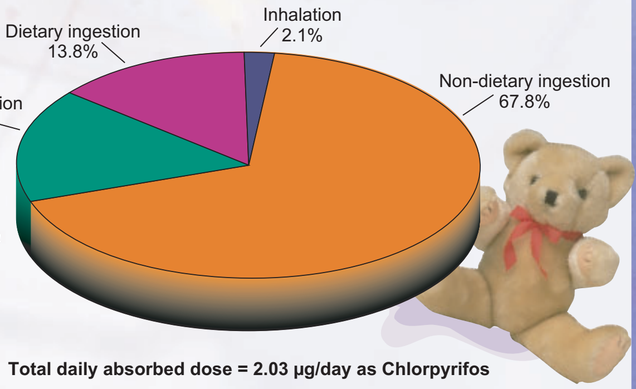


Figure 5

Pathway Contributions to Daily Absorbed Dose

Modeled results for MNCPES children's exposure to chlorpyrifos



Total daily absorbed dose = 2.03 µg/day as Chlorpyrifos